4. (twice amended) The microcapsule of claim 1, wherein the energy absorbing component comprises a spheroid within the microcapsule, and wherein the spheroid contains amyl alcohol, sorbitan [monooleate] monoleate, SMO-20, graphite/oil, or an oil, and wherein [the energy is] ultrasound energy is applied to the energy absorbing medium.

REMARKS

In response to the Office Action dated December 22, 1999, Applicants respectfully submit the amendments above and the remarks below for the Examiner's consideration.

Claims 1-59 and 69-71 are pending in the instant application. Claims 1-59 and 69-71 have been rejected. Claims 2-4 have been amended. No new matter has been added by these amendments to the claims.

I. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claims 2-4 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner suggests that the claims are vague with regard to recitation of an energy source, where the claim language "the energy source is a magnetic field, or radiofrequency or ultrasound" does not further limit the structure of the claimed microcapsule. Applicants have amended claims 2-4 to remove the language outlined by the Examiner. Accordingly, withdrawal of this rejection is respectfully requested.

II. Priority Date Under 35 U.S.C. § 120

The Examiner found the arguments set forth in the reply dated October 25, 1999 to be non-

persuasive. The Examiner again suggests that Applicants have not complied with one or more conditions for receiving the benefit of the earlier filing date of the parent application, now U.S. Patent No. 5,827,531. The Examiner suggests that the earlier U.S. application (now Patent 5,827,531) fails to teach specific features of the instant claims such as "energy absorbing components such as graphite, aluminum powder or TWEEN in contact with the outer membrane of the instant microcapsule, wherein said energy absorbing component is capable of melting at least a portion of the polymer membrane." The Examiner then suggests that the earlier application does not teach the "microcapsule comprising a drug or drug precursor." The Examiner also indicated he was unable to locate the teachings referred to by the Applicant at page 4 of the reply dated October 25, 1999. Applicants respectfully disagree with the Examiner's conclusions regarding priority for the instant application, for the following reasons.

As stated before, this application is a continuation-in-part of the parent application and was filed May 15, 1998, before the parent U.S. Patent No. 5,827,531 issued. This continuation-in-part application ("CIP") was filed during the lifetime of the parent application by the same applicants, repeated a substantial portion of the earlier application and added matter not disclosed in the earlier case, and references the parent application.

The present application has met all of the requirements necessary to claim the benefit of the filing date of its parent U.S. Patent No. 5,827,531. In fact, the MPEP explicitly states that:

> "an alleged continuation-in-part application **should be permitted** (bold added for emphasis only) to claim the benefit of the filing date of an earlier nonprovisional application if the alleged continuation-in-part application complies with the following formal requirements of 35 U.S.C. 120: (a) the first application and the alleged continuation-in-part application were filed with at least one common inventor; (b) the alleged continuation-in-part application filed before the patenting or abandonment of or termination of proceedings on the first application or an application similarly entitled to the benefit of the filing date of the first application; and (c) the alleged continuation-in-part application contains or is amended to contain specific reference to the earlier filed application."

Therefore, based on this specific guidance from MPEP 201.08, Applicants request that the Examiner reconsider the decision with respect to priority.

III. Rejection of Claims Under 35 U.S.C. § 102

A. Rejection Over Unger et al. (US Patent 5,853,752)

Applicants' arguments with regard to the previous rejection of claims 1-59 and 69-71 under 35 U.S.C. 102(e) as being anticipated by Unger et al. (US Patent 5,853,752; hereinafter referred to as Unger) were considered not persuasive by the Examiner and the rejection was maintained. The Examiner suggests that Unger specifically discloses incorporation of metal ions bound to lipid head groups which inherently act as an energy absorbing components, that ultrasound may be utilized not only to rupture but to cause thermal effects which may increase the rate of release of the active drug, and that other types of emulsifying agents such as oils and TWEEN can act as energy absorbing agents. Applicants respectfully traverse this rejection.

Applicants respectfully point out that invalidity for anticipation requires that there is no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. Scripps Clinic and Research Foundation v. Genentech, Inc., 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

Unger does not teach the encapsulation of an energy absorbing component that is specifically heated to a temperature beyond the melting point of the outer membrane by the absorption of energy. At column 38, lines 1-13, the section pointed to by the Examiner, Unger teaches that metal ions can be complexed to lipid head groups that increase the rate of formation of reactive oxygen intermediates when exposed to thermal irradiation, which describes a structurally different method for disruption of the membrane than the instant claims. Independent claim 1 states that one or more energy absorbing

components in an internal liquid phase is in contact with the outer membrane, not complexed with lipid groups. Being in contact and being complexed with a membrane are two very different states and the teaching of Unger would not lead one of ordinary to skill to assume that they are interchangeable. Unger teaches that the energy absorbing components disrupt the membrane by formation of reactive oxygen intermediates, and in column 38, lines 28-31, another section pointed to by the Examiner, that ultrasound may be used to increase the rate of chemical cleavage of an ester bond to form an active drug from a prodrug. In contrast, amended claim 1 recites "wherein the temperature of said energy absorbing component is increased by absorbing said energy to melt at least a portion of the polymer membrane." Therefore, the energy absorbing component is specifically heated to melt a portion of the polymer membrane, something that is not taught by Unger et al..

Unger does not teach that the energy absorbing materials can act to melt a hole in a portion of the outer membrane. In column 23, lines 35-39, Unger describes the use of metal oxides as materials to form a stabilizing center for gaseous precursors. It is the gaseous precursors, not the metal oxides, that are described as the method to disrupt the membrane. Likewise, Unger states in column 23, lines 40-66, that various oils can be used as emulsifying and/or solubilizing agents in conjunction with lipids or liposomes. These oils are described as materials to make the lipids easier to disperse, and, contrary to the Examiner's suggestion, **are not described as energy absorbing materials** to specifically melt a hole in a portion of the membrane.

Independent claims 1, 41, 44 and 69 each contain limitations related to temperature, none of which are taught or suggested by Unger et al. Amended claim 1 recites "wherein the temperature of said energy absorbing component is increased by absorbing said energy to melt at least a portion of the polymer membrane." Claim 41 recites at least two groups of microcapsules, each group containing a magnetic particle with a Curie point that is different from the Curie point of the magnetic point in the other group and where the Curie point of all magnetic particles is higher than the melting temperature of

the polymer membrane. Claim 44 recites "exposing the microcapsules to an energy source, effective to heat the internal component and to melt at least a portion of the polymer outer membrane and to release the drug." Amended claim 69 recites at least two groups of microcapsules, each having an outer membrane with a different melting point and where each melting point is less than the Curie point of the magnetic particles.

In addition, contrary to the Examiner's suggestion, Unger does not teach drug delivery by the specific heating of the energy absorbing components to melt a hole in a portion of the outer membrane. Rather than encapsulating an energy absorbing component to control the heating of a component to melt the outer membrane, Unger teaches the coordination of membrane composition with peak resonant frequency of a gaseous precursor to rupture the liposomes. For example, column 25, lines 15-22, states "liposomes prepared from dipalmitoylphosphatidylcholine are most preferred as they are selected for their ability to rupture on application of resonant frequency ultrasound, radiofrequency energy, (e.g. microwave), and/or echogenicity . . . ." This statement taken in conjunction with Unger's teaching of applying ultrasound at the peak resonance frequency of the therapeutic gaseous precursor-filled liposomes (see column 29, lines 31-41), clearly demonstrates that **Unger teaches the selection of the liposomal membrane components to provide the rupture properties for the delivery of drugs based on the gaseous precursor's peak resonance frequency. Unger does not teach the use of temperature to control the release of drug.** At column 29, lines 59-67, Unger actually teaches away from the use of higher wattage and time because of the increased heating.

As stated earlier, to anticipate a claim, the prior art reference must teach each and every claim limitation. The prior art reference of Unger et al. fails to teach each and every claim limitation as discussed above and thus cannot anticipate the claims. Accordingly, withdrawal of this rejection is respectfully requested.

B. Rejection Over Grinstaff et al. (US Patent 5,498,421)

Claims 1-43 and 69-71 were rejected under 35 U.S.C. 102(b) as being anticipated by Grinstaff et al. (US Patent 5,498,421; hereafter referred to as Grinstaff). Specifically, the Examiner suggests that Grinstaff teaches a polymeric shell for delivery of biologicals comprising an outer polymer membrane, an energy absorbing component such as metal particles selected from the group consisting of iron, iron oxide, and manganese, a biocompatible dispersing agent such as soybean oil, corn oil, cotton seed oil, and a drug selected from various therapeutic classes in a pharmaceutically acceptable carrier. Applicants respectfully traverse this rejection.

Grinstaff teaches compositions for delivery of biologicals that are composed of an outer polymer membrane made of a biocompatible material. Nowhere, however, does this patent teach or suggest the limitations of the claims of the instant invention which are a microcapsule where energy absorbing components such as graphite, aluminum powder or TWEEN are in contact with the outer membrane and where the property of the energy absorbing component is used to melt a portion of the polymer membrane as the method of drug delivery. Applicants reviewed each of the sections of the patent specifically pointed to by the Examiner as well and found no teaching of use of energy absorbing components as suggested by the Examiner. Therefore, Grinstaff fails to teach the limitations of the instant claims and cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

C. Rejection of Claims Over McGinity et al. (US Patent 5,288,502)

Claims 1, 3-9, 11, 21-23, 31-35, and 40-43 were rejected under 35 U.S.C. 102(b) as being anticipated by McGinity et al. (US Patent 5,288,502; hereafter referred to as McGinity). Specifically, the Examiner suggests that McGinity discloses multi-phase polymeric microspheres containing molecular compound dispersed in a polymeric matrix where the microsphere has a diameter of 50 to 200 microns

and comprises a biocompatible polymer surrounding a fixed oil that contains a drug. Applicants respectfully traverse this rejection of the claims.

McGinity does not teach the use of an external energy source to heat an energy absorbing compound to melt a hole in the outer polymer membrane. McGinity describes polymeric microspheres with a molecular compound in microemulsions dispersed throughout a polymer matrix. A biodegradable polymer surrounds a fixed oil or oil/aqueous emulsion containing a water-soluble or insoluble drug; see column 3, lines 61-67. The method of drug delivery is biological degradation of the polymer for a slow release of the drug-containing microemulsions; see column 9, lines 11-14 and column 12, lines 55-68. McGinity does not describe at all the use of an energy absorbing compound that is specifically heated to melt a hole in an outer polymer membrane to disrupt the microsphere. Therefore, McGinity fails to teach each and every limitation of the instant claims and cannot anticipate the instant invention. Accordingly, withdrawal of this rejection is respectfully requested.

D. Rejection of Claims Over Tsuei et al. (US patent 5,589,194)

Claims 1-4, 6-8, 21, 24, 26-27, 36, 40-44, and 69-71 were rejected under 35 U.S.C. 102(b) as being anticipated by Tsuei et al. (US Patent 5,589,194; hereafter referred to as Tsuei). Specifically, the Examiner suggests that Tsuei teaches microcapsules comprising an outer polymer membrane, an energy absorbing component and a drug as well as incorporation of various fillers such as graphite and energy absorbing particles in their microspheres. Further, the Examiner suggests that Tsuei disclose methods of releasing the active drug from the microcapsule core comprising applying energy so that the energy absorbed by the energy absorbing compounds of the microcapsule can further melt the outer membrane and release the active component. Applicants respectfully traverse this rejection.

Tsuei does not teach microcapsules with an outer polymer membrane, surrounding one or more internal immiscible liquid phases as claimed in the instant invention. In column 2, lines 26-33, Tsuei

describes the creation of a solid phase in which the active component is dissolved; the solution is then injected into a quenching liquid to solidify the material into microspheres. Further, Tsuei does not teach the use of an energy absorbing component that is specifically heated to melt a hole in a portion of the outer polymer membrane. Tsuei describes the use of filler components such as graphite to be used to reduce the cost of the matrix, to modify the active component, or to slow the release process of the component by providing a block to diffusion; see column 5, lines 28-37. Additional components, such as magnetic particles or energy absorbing particles, are described that can be incorporated at the outer surface of the microcapsule (column 6, lines 50-57) and can aid in melting of the solid matrix on direct heating (column 10, lines 20-25). However, these particles at the outer surface are described as aiding the melting of the entire outer surface of the solid matrix at once. Tsuei does not describe the use of an energy absorbing particle that is specifically heated to melt a hole in a portion of the outer polymer membrane as claimed in the instant invention; further, Tsuei does not describe the use of an outer polymer membrane at all. Therefore, contrary to the Examiner's suggestion Tsuei does not teach or suggest the limitations of the instant invention and cannot anticipate the instant invention. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-59 and 69-71 were rejected under 35 U.S.C. 103(a) as being unpatentable over Tsuei et al. (US Patent 5,589,194) and Unger et al. (US Patent 5,853,752). The Examiner suggests it would have been *prima facie* obvious for one of ordinary skill in the art to develop a microcapsule comprising various types of pharmaceutical agents as taught by Unger et al. to create microcapsules that by methods taught by both Tsuei and Unger, and although Tsuei does not specifically teach methods utilizing various energy sources they suggest use of an external energy source for releasing active drug from the microcapsules and it would have been obvious to one of ordinary skill to apply various energy sources as

taught by Unger et al. Applicants respectfully traverse this rejection.

As discussed *supra* in Section III, each of these primary references cited by the Examiner fails to teach the instant invention and all of its limitations as claimed. Unger does not teach the encapsulation of an energy absorbing component that is specifically heated to a temperature beyond the melting point of the outer membrane by the absorption of energy. The claims of the instant invention recite a "wherein the temperature of said energy absorbing component is increased by absorbing said energy to melt at least a portion of the polymer membrane." Therefore, the energy absorbing component is specifically heated to melt a portion of the polymer membrane, something that is not taught by Unger et al.. Rather than encapsulating an energy absorbing component to control the heating of a component to melt the outer membrane, Unger teaches the coordination of membrane composition with peak resonant frequency of a gaseous precursor to rupture the liposomes. Also as discussed *supra* in Section III, Tsuei et al. fail to teach the limitations of the invention as claimed. Tsuei does not teach microcapsules with an outer polymer membrane, surrounding one or more internal immiscible liquid phases as claimed, nor use of an energy absorbing component that is specifically heated to melt a hole in a portion of the outer polymer membrane. In fact, Tsuei et al. teaches microcapsules that are a solid phase with an active component dissolved in that solid phase, which is very different than the microcapsules of the instant invention.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as not one of the cited references, either alone or in combination, teaches or suggests microcapsules with an outer polymer membrane, surrounding one or more internal immiscible liquid phases and use of energy absorbing components to melt a portion of the outer

membrane and release an active component contained in the internal phases. Therefore, the cited references would not motivate one to make the microcapsules of the instant invention and cannot render the instant claimed invention obvious. Therefore, withdrawal of this rejection is respectfully requested.

V. New Matter

Claims 69-71 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the recitation of "compositions comprising at least two groups of microcapsules, wherein a first group has a polymer outer membrane with a different melting point than microcapsules of a second group, and further wherein both first and second melting points are lower than the Curie point of the magnetic particles" is not supported in the disclosure. Applicants respectfully disagree with the Examiner's conclusions.

Applicants respectfully point out that at pages 45-46 of the specification as filed, the microcapsules as described in claims 69-71 are discussed. For example, at page 45, lines 27-31, and page 46, lines 1-9, the microcapsule of claim 69 is described in terms as claimed with the Curie point being a distinguishing factor wherein the Curie point of the magnetic particles is higher than that of the polymer outer membrane melting point. It is within the knowledge of one of skill in the art to choose such components or polymers. The key feature is knowledge of the melting point and assuring that it is lower than the Curie pont of the particles. Therefore, the specification as filed would cover polymer outer membranes made from different materials and having different melting points. The use of this combination of microcapsules with different properties is described at page 41, lines 1-3, of the specification as filed where the use of the microcapsules to deliver multiple drugs or several pulses of drug is described. In particular, the release of pulses of drug could be accomplished with the invention of

claims 69-71. Then, at page 65, lines 27-31, the specification states that variations and modifications of the invention are possible and within the skill of one in the art. Therefore, claims 69-71, which only combine two types of microcapsules made in accordance with the teachings of the specification but with outer polymer membranes having different melting points would be within the scope of the teachings of the specification as filed. Withdrawal of this rejection is respectfully requested.

V. Conclusions

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited. If the Examiner has any questions or suggestions concerning the application or allowance of any claim thereof, or feels that an interview would advance the examination process, the Examiner is requested to call the Applicants' undersigned attorney at the direct dial number printed below.

Respectfully,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

March 16, 2000.

James M. Cate